REMARKS

Amendments to the Claims

Claims 1-3, 12, and 15 have been cancelled. Claims 4, 5, 7-10 have been amended to depend from claim 13. Claim 14 has been amended to delete the characterization of the levels of circulating tumor cells in the blood and to recite a markush group of hematologic malignancies. New claim 28 has been added and is directed to a method of treating chronic lymphocytic leukemia. Support for new claim 28 is found in applicants' specification *inter alia* at page 3, lines 15-19 and page 4, lines 10-15.

Objection to the Specification

The Examiner has indicated that the trademark Rituxan® should be capitalized wherever it appears and be accompanied by the generic terminology. Applicants have corrected all such references throughout the specification in response to the Examiner's request.

35 U.S.C. §112 Rejection

The Examiner has maintained the rejection of claims 1-12 and 14-18 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner urges that applicants' amendment of claims 1, 12 and 14 to include the recitation "hematologic malignancy is characterized by a white blood cell count from 4 x 10^9 to about 200 x 10^9 white blood cells per liter of blood" introduces new matter.

Applicants submit that the recitations in previously presented claims 1, 12, and 14 of ranges of white blood cell counts are described in the present specification. Applicants, however, also note that certain specific types of hematologic malignancies referenced in the

specification are well known in the art. The present claims have been amended to employ these art-recognized terms. Since the amendments made herewith obviate the need for further consideration of the circulating white blood cells ranges, the Examiner's rejection of the claims is rendered moot. Accordingly, the Examiner is requested to withdraw the rejection of the claims on this basis.

35 U.S.C. §102(e) Rejection

The Examiner has rejected claim 13 under 35 U.S.C. 102(e) as anticipated by U.S. Patent No. 6,090,365 ("the Kaminski et al. patent"). The Examiner maintains that the Kaminski et al. patent discloses methods for treatment of chronic lymphocytic leukemia, chronic myeloblastic leukemia and lymphomas by administration of a B-cell specific antibody, antibody B1. The Examiner urges that it is reasonable to conclude that B-prolymphocytic leukemia and transformed non-Hodgkin's lymphoma would also be treated using the disclosed methodology to achieve the reduction in circulating tumor cells in light of the patent's disclosure of the successful treatment of the listed leukemias and lymphomas. Applicants respectfully traverse this rejection.

Claim 13, as amended, relates to a method of treating a hematologic malignancy selected from the group consisting of a B-prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL) and transformed non-Hodgkin's lymphoma by administering a therapeutically effective amount of an anti-CD20 antibody or antigen-binding fragment thereof, said amount being effective to achieve a reduction in circulating tumor cells.

To anticipate, a prior art reference must disclose each and every element of the claimed invention as set forth in the rejected claim. Scripps Clinic & Res. Found. v. Genentech, Inc., 927 F.2d 1565, 1576 (Fed. Cir. 1991). The Kaminski patent fails to teach every element of applicants' invention as set forth in claim 13, and thus does not anticipate the claim.

The invention disclosed in the Kaminski patent relates to therapy of lymphoma using antibodies directed to an antigen present on the surface of lymphoma cells. The portions of the Kaminski specification cited by the Examiner do not teach treatment of CLL and chronic myeloblastic leukemia (CML) through administration of a B-cell specific antibody (specifically the antibody B1). At col. 5, lines 25-35, Kaminski discloses that the invention provides methods for immunotherapy of lymphoma which employ the B1 antibody. Column 7, lines 24-47 cited by the Examiner relates to the treatment of B cell lymphoma, not CLL or CML. Column 13, lines 40-61 cited by the Examiner discloses treatment of non-Hodgkin's lymphoma patients.

The only reference in the Kaminski patent to CLL and CML occurs at column 6, lines 4-7. There, the patent cites CLL and CML as examples of cancers which are clonal from cells of B cell lineage that can be treated with antibodies that bind antigens other than CD19 and CD20. As set forth, the passage reads:

> Also, the invention is not limited to the CD19 and CD20 antibodies. Rather, the invention also encompasses the use of antibodies which are identify antigens associated with cells of the B cell lineage to treat cancers which are clonal from such cells. Examples of such antibodies are B2, B3, B4 (HD-237), and J5, in addition to B1. Examples of such cancers are ALL, CLL, Hairy Cell leukemia, and chronic myeloblastic leukemias in a blast crisis stage, in addition to lymphomas.

As such, the Kaminski patent does not teach treatment of B-PLL, CLL or transformed non-Hodgkin's lymphoma with an antibody that binds the CD20 antigen, or fragment thereof as set

forth in claim 13. Accordingly, the Kaminski patent does not anticipate claim 13. The Examiner is requested to withdraw the rejection of claim 13 on this basis.

Rejection Under 35 U.S.C. §102(a)

The Examiner has rejected claims 1-4, 6, 7, 9, and 12-17 under 35 U.S.C. 102(a) as anticipated by McLaughlin et al. (Journal of Clinical Oncology 16(8): 2825-2833, August 1998/IDS reference B1, submitted October 19, 2004). The Examiner urges that McLaughlin discloses a method of treating patients with relapsed indolent lymphoma and patients with chronic lymphocytic leukemia having less than 5 x 10^9/L lymphocytes comprising the administration of a chimeric anti-CD20 monoclonal antibody, rituximab. The Examiner further urges that CLL patients with 4 x 10^9 are within applicants' stated range listed in claim 1 and further urges that the administration of the antibody would result in a reduction in circulating tumor cells.

Applicants have cancelled claims 1 and 12 and have amended claim 14 to no longer recite the characterization of the levels of circulating tumor cells in the blood. Accordingly, applicants will address the Examiner's rejection of claims 13 and 14 and claims dependent thereon.

Applicants submit that the Examiner's position that McLaughlin discloses a method of treating patients with CLL having less than 5 x 10^9 /L with rituximab is in error. The McLaughlin trial was conducted on patients with relapsed low grade or follicular lymphoma. At page 2926, first column the eligibility criteria for the trial are set forth as follows:

> Adult patients with relapsed low grade or follicular B-cell lymphoma, histologically confirmed and positive for CD20, were eligible. Patients with chronic lymphocytic leukemia (lymphocytes > 5 x 10^9/L) were excluded. (emphasis added).

On the same page, under the heading "Patient Features" it is disclosed that of the 166 patients enrolled at 31 centers:

> There were 33 with small lymphocytic lymphoma (SL), 67 with follicular small cleaved, 53 with follicular mixed, three with other low grade lymphoma variants, and 10 with follicular large cell.

Thus, McLaughlin does not disclose treatment of patients with chronic lymphocytic leukemia, but in fact discloses treatment of patients that do not present with this indication. As set forth above, to anticipate a claimed invention under §102, a reference must teach each and every element of the claimed invention. Since the McLaughlin article fails to teach a method of treating a hematologic malignancy selected from the group consisting of B-prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL) and transformed non-Hodgkin's lymphoma by administering a therapeutically effective amount of an antibody that binds the CD20 antigen, or fragment thereof, to achieve a reduction in circulating tumor cells as set forth in claim 13 or a method of avoiding or reducing the toxicity associated with administration of a therapeutic antibody to patients have such a hematologic malignancy as set forth in claim 14, it cannot anticipate the rejected claims. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection of the claims on this basis.

35 U.S.C. §103 Rejection

The Examiner has rejected claims 1-18 under 35 U.S.C. §103(a) as unpatentable over McLaughlin et al. in view of USP 6,682,734 ("the 734 patent") and EP document 510,949A2 ("the 949 application"). The Examiner has taken the position that the '734 patent teaches the administration of effective dosages or therapeutically effective amounts of immunologically active chimeric anti-CD20 antibodies from about 0.001 to about 30 mg/kg body weight and suggests that the skilled artisan could easily assess a suitable dosage for a particular patient. The

Examiner further urges that the patent teaches treatment with chemotherapeutic agents such as cyclophosphamide, vincristine, prednisone and doxorubicin(CHOP) and radionuclides. The Examiner maintains that the '949 application teaches conjugate moieties comprising antibodies and interleukins 1-10, GM-CSF, TNF and interferons and their subsequent administration for treatment of leukemias and lymphomas. The Examiner maintains that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of McLaughlin, the '734 patent and the '949 application to efficaciously treat cancer and that there was motivation to do so based on knowledge in the art. Applicants traverse the Examiner's rejection of claims 1-18 on this basis.

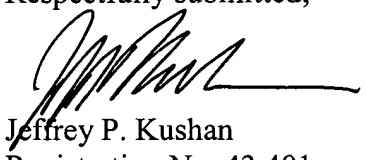
Applicants respectfully submit that the present claims define a method that is not obvious under §103 from the cited prior art. To properly reject a claim as obvious under §103, the Examiner must present evidence and arguments that establish a *prima facie* showing that the claimed invention is obvious over the prior art. To establish a *prima facie* case of obviousness, the prior art references when combined must teach or suggest all the claim limitations. *See* MPEP §2143. As set forth above, the McLaughlin article fails to teach a method of treating a hematologic malignancy selected from the group consisting of B-prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL) and transformed non-Hodgkin's lymphoma by administering a therapeutically effective amount of an antibody that binds the CD20 antigen, or fragment thereof, to achieve a reduction in circulating tumor cells as set forth in claim 13 or a method of avoiding or reducing the toxicity associated with administration of a therapeutic antibody to patients have such a hematologic malignancy as set forth in claim 14. Rather, the McLaughlin trial included patients with relapsed low grade or follicular lymphoma. The '734 patent and the EP '949 application fail to teach the claimed method of treating B-prolymphocytic

leukemia, chronic lymphocytic leukemia and transformed non-Hodgkin's lymphoma as set forth in claim 13 or the claimed method of avoiding or reducing the toxicity associated with administration of a therapeutic antibody to patients having such hematologic malignancy as set forth in claim 14, as amended, and therefore fail to cure the defect of the primary cited reference. Accordingly, even in combination, the references fail to render obvious the claimed invention because in combination the references fail to teach this claim limitation. The Examiner also is not citing these secondary references as teaching this claim limitation. Rather, the Examiner has cited the '734 patent as teaching effective dosages or therapeutically effective amounts of antibodies to the CD20 antigen and treatment with chemotherapeutic agents. The EP '949 document has been cited as teaching conjugate moieties comprising antibodies and interleukins and interferons for treatment of leukemias and lymphomas. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness of claims 1-18 over the cited references. Applicants request that the Examiner withdraw the rejection of the pending rejected claims on this basis.

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully submit that all pending claims as currently presented are in condition for allowance. If, for any reason, the Examiner disagrees, please call the undersigned attorney at 202-736-8914 so that Applicants may attempt to resolve any matter still outstanding before issuing another action. Favorable reconsideration is respectfully requested.

Respectfully submitted,



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Date: May 2, 2005